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Developing targeted liposomal vaccines

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Pattern recognition receptors, including the Toll-like receptors (TLRs), are important in the induction and activation of two critical arms of the host defense to pathogens and microorganisms; the rapid innate immune response (as characterized by the production of Th1 cytokines and type 1 interferons) and the adaptive immune response. Through this activation, ligands and agonists of TLRs may offer advantages as vaccine adjuvants offering enhanced immunotherapeutic efficacy. However, incorporation or encapsulation of these TLR agonists within delivery systems, such as liposomes, would be beneficial due the importance of local maintenance of the agonist at the site of antigen administration for optimal adjuvant activity to be achieved, without systemic distribution throughout the host. Resiquimod is a small (water-soluble) agonist of the endosome-located Toll-like receptor 7 (TLR7), therefore upon injection it will rapidly distribute throughout the body rather than staying at the injection site. In this present study, resiquimod has been chemically synthesized with DSPE lipid to form a lipid=TLR agonist conjugate before further being incorporated within the cationic liposomes composed of dimethyl dioctadecyl ammonium bromide (DDA) and the immune-stimulatory glycolipid trehalose 6,6′ -dibehenate (TDB). The liposomes formulated with and without the conjugated TLR7 ligand displayed similar vesicle characteristics and conjugation of resiquimod resulted in strong retention of both resiquimod, as well as adsorbing the TB subunit vaccine Ag85B-ESAT6-Rv2660c (H56). Following vaccine delivery through the intramuscular route a depot at the site of injection was formed promoting controlled release and drainage of delivery system and TLR agonist to the popliteal lymph node. Immunization studies have shown that this bio-distribution profile translates into increased Th1 responses, as well as down-regulation of Th2 responses both at the spleen, injection site and draining popliteal lymph node.

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